UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/977,693	10/16/2001	Jonathan S. Stamler	Duke 1931	3762

7590 04/18/2006

Ivor R. Elrifi, Esq.
Mintz, Levin, Cohn, Ferris Glovsky and Popeo PC
One Financial Center
Boston, MA 02111

EXAMINER	
SCHLAPKOHL, WALTER	
ART UNIT	**PAPER NUMBER**
1636	

DATE MAILED: 04/18/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/977,693	STAMLER, JONATHAN S.	
	Examiner	Art Unit	
	Walter Schlapkohl	1636	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *10 February 2006*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-3,5-9 and 11-17* is/are pending in the application.

4a) Of the above claim(s) *11-12* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-3,5-9 and 13-17* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *6/2/03 & 1/10/02*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

The Examiner for your application in the USPTO has changed. To aid in correlating any papers for this application, all further correspondence regarding this application should be directed to Walter Schlapkohl in Art Unit 1636 whose contact information can be found in the conclusion of this Office action.

Receipt is acknowledged of the papers filed 2/10/2006 in which claims 1 and 5 were amended and claims 13-17 were added. Claims 1-3, 5-9, and 11-17 are pending. Claims 1-3, 5-9 and 13-17 are under examination. Claims 11-12 are withdrawn.

Any rejections made within the prior Office action which are not recited herein are hereby withdrawn.

Continued Examination Under 37 CFR 1.114

A request for continued examination under 37 CFR 1.114 was filed in this application after appeal to the Board of Patent Appeals and Interferences, but prior to a decision on the appeal. Since this application is eligible for continued examination under 37 CFR 1.114 and the fee set forth in 37 CFR 1.17(e) has been timely paid, the appeal has been withdrawn pursuant to 37 CFR 1.114 and prosecution in this application has been reopened pursuant to 37 CFR 1.114. Applicant's submission filed on 2/10/2006 has been entered.

Claim Objections

Claim 1 recites "a simulated redox perturbation" in lines 7-8. It appears that claim 1 should recite "a simulated redox state perturbation."

Claim 16 is objected to because of the following informalities: claim 16 recites "[t]he method of Claim 15 where the oxygen tensions employed are in step (b) range from 0.1 mm Hg to 145 mm Hg" in lines 1-2. It appears that claim 16 should recite "[t]he method of Claim 15 where the oxygen tensions employed [[are]] in step (b) range from 0.1 mm Hg to 145 mm Hg."

Appropriate correction is required.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 2, 5-6 and 13-14, and therefore dependent claims 7-9, and 15-17, are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 2 recites "[t]he method of Claim 1, wherein the simulated redox state perturbation is generated by a process selected from the group consisting of : variation of glucose concentration from physiological state, presence of metal ions, alteration in NADH ratio, and oxygen concentrations less than room air" in lines 1-5. Claim 2 is vague and indefinite in that it is unclear how the NADH ratio is determined? Does Applicant intend a change in NADH concentration, or is applicant comparing NADH levels to some other form of NADH (e.g. NAD+)?

Claims 5 and 13 recite "where the screening is performed in the presence of decreased oxygen tension" in lines 7-8 and lines 4-5, respectively. Claims 5 and 13 are vague and indefinite in the meets and bounds of "decreased" are unclear. Does "decreased" refer to any oxygen tension as long as it is smaller in value than that of the room air of step (a), or is the "decreased" oxygen tension in comparison to some other tension?

Claim 6 recites "[t]he method of Claim 5 where at least one protein employed in the determination is associated with a physiological process or a pathophysiological process" in lines 1-3. Claim 6 is vague and indefinite in that "the determination" lacks clear and positive antecedent basis. Does "the determination" refer to an observed protein-protein

interaction from step (b) or to a difference in protein-protein interactions as determined in step (c)?

Similarly, claim 14 recites "[t]he method of Claim 13 where at least one protein employed in the determination is associated with a physiological process or a pathophysiological process" in lines 1-2. Claim 14 is vague and indefinite in that "the determination" lacks clear and positive antecedent basis. Does "the determination" refer to an observed protein-protein interaction from step (b) or to a difference in protein-protein interactions as determined in step (c)?

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-3, 5-9 and 13-17 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claims contain subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the

inventors, at the time the application was filed, had possession of the claimed invention. **This is a new matter rejection.**

The specification as originally filed does not provide support for the invention as now claimed: "where the plurality of proteins are screened concurrently". The specification does not provide sufficient blazemarks nor direction for the methods encompassed by the above-mentioned limitation, as currently recited. The instant claims now recite a limitation, which was not clearly disclosed in the specification as filed, and now changes the scope of the instant disclosure as filed. Such a limitation recited in the present claims, which did not appear in the specification as filed, introduces new concepts and violates the description requirement of the first paragraph of 35 U.S.C. 112. Applicant is invited to point out where in the instant specification the phrase "where the plurality of proteins are screened concurrently" can be found, either in the context of protein-protein interactions or in the context of protein levels.

Furthermore, new claims 13-17 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement (new matter) on the grounds that the specification does not provide sufficient blazemarks nor direction for the recited method steps. The specification

discloses that "protein interaction(s)"--which is used in the specification to mean the same as the broadly-defined "proteomic interaction(s)" and therefore includes a "change in level or expression of proteins" (page 4, lines 10-12)--can be correlated with oxygen tension. However, the specification does not disclose such a method wherein the protein levels of a plurality of proteins are screened, wherein the screening is performed in room air, and further wherein the screening for protein levels is further performed in decreased oxygen tension, and further wherein the protein level(s) at room air and the protein level(s) at decreased oxygen tension were correlated. Neither does the specification disclose such methods wherein such determinations are associated with a physiological process (claim 14), nor such a method with different oxygen tensions being employed in each determination (claim 15), nor such a method wherein the oxygen tensions employed range from 0.1 mm Hg to 145 mm Hg (claim 16), nor such a method wherein the protein levels are used to identify protein functions associatd with a pathophysiological process. Indeed, these limitations are all disclosed in the specification, but only in the context of protein-protein interactions, not protein levels.

Response to Arguments

Applicant's arguments with regard to the new matter rejection made in the Office action mailed 4/18/2005 have been rendered moot by Applicant's amendment.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless -
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.
>
> (e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

Claims 1-2, 5-6, 9 and 13-14 are rejected under 35 U.S.C. 102(b) as being anticipated by Tucci et al (Journal of Endocrinology 157:13-24, 1998). **This is a new rejection.**

Tucci et al teach a method of establishing a protein-protein interaction map comprising (a) screening for a protein-protein interaction between at least one protein and a plurality

of proteins, wherein the screening is performed in the absence of a simulated redox state perturbation and wherein the plurality of proteins are screened concurrently; (b) screening for a protein-protein interaction between the at least one protein and a plurality of proteins where the screening is performed in the presence of a stimulated redox state perturbation and wherein the plurality of proteins are screened concurrently; and (c) generating the protein-protein interaction map by identifying at least one different protein-protein interaction between (a) and (b). Tucci et al teach such a "map" in the form of a Western blot in which bovine aortic endothelial cells (BAEC) and bovine pulmonary artery endothelial cells (BPAEC) are cultured in 21% oxygen (room air) or exposed to hypoxia (0% oxygen) for 24, 48 and 72 hours (see Figure 2, paragraph bridging pages 14 and 15, Figure 3, and the second and third full paragraphs on page 15). In Figure 2, Tucci et al utilize a radio-labeled IGF-II protein (^{125}I-IGF-II) to screen for protein-protein interactions between IGF-II and variants of IGFBP in the absence of a simulated redox state perturbation (21% oxygen) and in the presence of a simulated redox perturbation (0% oxygen). This screening was performed concurrently on the same blot. Generation of the Western ligand blot led to the identification of at least one different

protein-protein interaction between (a) and (b) as noted in, e.g., Figure 3, wherein the protein-protein interaction between IGF-II and IGFBP-3 was decreased at 72 hours of hypoxic conditions. Regarding claim 6, Tucci et al teach that at least one protein employed in the determination is associated with a physiological process or a pathophysiological process (see reference to the role of IGFs and IGFBPs in paragraph bridging pages 13-14). Regarding claim 9, the different interactions are used to identify protein functions associated with a pathophysiological process, i.e. hypoxemia (see Introduction on page 13). Regarding claims 13-14, the same Figure 2 and text citations as noted above also teach such a method whereby protein levels are correlated to oxygen tension and wherein at least one protein employed in the determination is associated with a physiological or pathophysiological process.

Claims 13-17 are rejected under 35 U.S.C. 102(e) as being anticipated by Loehrlein et al (Patent Application Publication No. US 2002/0160361). **This is a new rejection.**

Loehrlein et al teach a method of correlating protein levels with oxygen tension comprising (a) screening for protein levels of a plurality of proteins, where the screening is performed in room air and in the presence of decreased oxygen

tension and where the plurality of proteins are screened concurrently. Loehrlein et al teach correlating the protein level(s) with oxygen tension by identifying at least one different protein level between (a) and (b) (see entire document, especially page 2, paragraph 16; and page 8, paragraph 95). Note that obtaining cDNAs from a plurality of samples for a plurality of target sequences is a measure of gene expression and therefore an indirect measurement of protein levels. Furthermore, "gene expression" has been defined within the reference to include translation into protein (page 4, paragraph 46). The Loehrlein et al reference teaches that treatments such as "oxygen concentration" (e.g. hypoxia) may induce differences in gene expression and that such treatments "can be imposed for various times and at various concentrations," thus meeting the claim limitations of claim 15 (page 8, paragraph 95). The proteins employed in the determination are associated with a pathophysiological process as indicated at page 6, paragraph 84. While Loehrlein does not explicitly teach such a method wherein the oxygen tensions employed are in the range from 0.1 mm Hg to 145 mm Hg, the altered conditions taught by Loehrlein et al include "various concentrations" of hypoxia, which includes oxygen tensions within the recited range.

Response to Arguments

Applicant's arguments with regard to the rejection of record made under 35 U.S.C. §102 are rendered moot by Applicant's amendment.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 1-3 and 5-9 and 13-17 are rejected under 35 U.S.C. 103(a) as being unpatentable over Tucci et al (cited above) in view of Livingston et al (WO 00/74725 A1).

Briefly, Tucci et al teach a method of establishing a protein-protein interaction map comprising (a) screening for a protein-protein interaction between at least one protein and a plurality of proteins, where the screening is performed in the *absence* (step (a)) and in the *presence* (step (b) of a simulated redox state perturbation and where the plurality of proteins are screened concurrently; and then generating the protein-protein

interaction map by identifying at least one different protein-protein interaction between (a) and (b) (step (c)). Tucci et al teach such a "map" in the form of a Western blot in which bovine aortic endothelial cells (BAEC) and bovine pulmonary artery endothelial cells (BPAEC) are cultured in 21% oxygen (room air = 21% oxygen = 160 mm Hg) or exposed to hypoxia (0% oxygen) for 24, 48 and 72 hours (see Figure 2, paragraph bridging pages 14 and 15, Figure 3, and the second and third full paragraphs on page 15). The protein-protein/protein level interaction "map" generated by Tucci et al correlates protein-protein interactions/protein levels to gain insight into the physiological processes related to hypoxemia, "one of the most frequent and common insults to the vascular endothelium (page 13, first paragraph). Tucci et al further teach that vascular endothelial cells "tolerate acute hypoxia (0% oxygen) for periods up to five days and chronic hypoxia (3% oxygen ≈ 23 mmHg) for periods up to several months (page 13, first paragraph).

Tucci et al do not teach such a method wherein the simulated redox state perturbation is generated by addition of redox state modifier molecule selected from the group consisting of superoxide, peroxide, hydrogen peroxide, alkoxides, sulfoxides, brominating species, chlorinating species,

nitrosating molecules, nitric oxide, S-nitrosothiols, nitrating molecules, peroxynitrite, NO^- generating molecules, glutathione-regulating enzymes, NADH-regulating enzymes, and flavin-regulating enzymes. Neither do Tucci et al teach such a method wherein a plurality of determinations are made with different oxygen tensions being employed in each determination or wherein the oxygen tensions employed are in the range from 0.1 mm Hg to 145 mm Hg.

Livingston et al teach methods for identifying compounds that can be used to modify transcriptional responses and protein-protein interactions in response to hypoxia, as well as the use of such compounds (see entire document, especially Abstract and the paragraph bridging pages 13-14). Specifically, Livingston et al teach such methods wherein cells are plated in multiwell format, candidate compounds are added and then the cells are made hypoxic either by "true" hypoxia (e.g., 1% oxygen ≈ 8 mm Hg) or by adding deferoxamine or the chlorinating species, $CoCl_2$ (page 13, lines 6-10). Livingston et al further teach that the hypoxic conditions to which cells are exposed can be by exposure to low oxygen levels, or induced chemically, e.g. by deferoxamin or cobalt chloride (Page 3 lines 22-24). Livingston et al also teach that oxygen tension in the tumor

microenvironment drops as the passive diffusional capacity of the existing blood supply is surpassed (page 1, lines 12-16).

It would have been obvious for one of ordinary skill in the art to combine the method of Tucci et al with the method hypoxic conditions/chlorinating species of Livingston because both references teach methods of assessing differences in gene expression/protein levels in the presence and absence of hypoxic conditions.

One of ordinary skill in the art would have been motivated to combine the references and to utilize different or multiple hypoxic or redox state perturbing conditions depending upon the intended design of the method, i.e., 0% oxygen for up to five days for acute hypoxia stimulation or 3% oxygen for up to several months for chronic hypoxia as taught by Tucci et al, or "true" hypoxic conditions (1% oxygen) or simulated hypoxic conditions (stimulation with cobalt chloride) as taught by Livingston et al.

Absent evidence to the contrary and based upon the prior art, one or ordinary skill in the art would have had a reasonable expectation of success when combining the methods of Tucci et al with those of Livingston et al.

Response to Arguments

Applicant's arguments with regard to the rejection of record made under 35 U.S.C. §103 are rendered moot by Applicant's amendment.

Conclusion

Certain papers related to this application may be submitted to the Art Unit 1636 by facsimile transmission. The faxing of such papers must conform with the notices published in the Official Gazette, 1156 OG 61 (November 16, 1993) and 1157 OG 94 (December 28, 1993) (see 37 C.F.R. § 1.6(d)). The official fax telephone number for the Group is (571) 273-8300. Note: If Applicant *does* submit a paper by fax, the original signed copy should be retained by Applicant or Applicant's representative. NO DUPLICATE COPIES SHOULD BE SUBMITTED so as to avoid the processing of duplicate papers in the Office.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to (571) 272-0547.

Patent applicants with problems or questions regarding electronic images that can be viewed in the Patent Application Information Retrieval system (PAIR) can now contact the USPTO's Patent Electronic Business Center (Patent EBC) for assistance. Representatives are available to answer your questions daily from 6 am to midnight (EST). The toll free number is (866) 217-9197. When calling please have your application serial or patent number, the type of document you are having an image problem with, the number of pages and the specific nature of the

problem. The Patent Electronic Business Center will notify applicants of the resolution of the problem within 5-7 business days. Applicants can also check PAIR to confirm that the problem has been corrected. The USPTO's Patent Electronic Business Center is a complete service center supporting all patent business on the Internet. The USPTO's PAIR system provides Internet-based access to patent applications to view the scanned images of their own application file folder(s) as well as general patent information available to the public.

For all other customer support, please call the USPTO Call Center (UCC) at (800) 786-9199.

Any inquiry concerning rejections or objections in this communication or earlier communications from the examiner should be directed to Walter Schlapkohl whose telephone number is (571) 272-4439. The examiner can normally be reached on Monday through Thursday from 8:30 AM to 6:00 PM. The examiner can also be reached on alternate Fridays.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Dr. Remy Yucel can be reached at (571) 272-0781.

Walter A. Schlapkohl, Ph.D.
Patent Examiner
Art Unit 1636

April 11, 2006

NANCY VOGEL
PRIMARY EXAMINER